THE PSYCHIATRIC CLINICS OF NORTH AMERICA

Post-Traumatic Stress Disorder

DAVID A. TOMB, MD, GUEST EDITOR

VOLUME 17 • NUMBER 2 • JUNE 1994

W.B. SAUNDERS COMPANY
A Division of Harcourt Brace & Company
PHILADELPHIA LONDON TORONTO MONTREAL SYDNEY TOKYO

W.B. Saunders Company
A Division of
Harcourt Brace & Company

The Curtis Center
Independence Square West
Philadelphia, Pennsylvania 19106-3399

The Psychiatric Clinics of North America is covered in *Index Medicus, Current Contents/Social and Behavioral Sciences, Social Science Citation Index, Excerpta Medica,* and PsycINFO.

THE PSYCHIATRIC CLINICS OF NORTH AMERICA **ISSN 0193–953X**
June 1994 **Volume 17—Number 2**

The Psychiatric Clinics of North America (ISSN 0193–953X) is published quarterly by W.B. Saunders Company. Corporate and Editorial Offices: The Curtis Center, Independence Square West, Philadelphia, PA 19106-3399. Accounting and Circulation Offices: 6277 Sea Harbor Drive, Orlando, FL 32887-4800. Second-class postage paid at Orlando, FL 32862, and additional mailing offices. Subscription price is $89.00 per year (U.S. individuals), $110.00 per year (U.S. institutions), $116.00 per year (foreign individuals), and $123.00 per year (foreign institutions). Foreign air speed delivery for all *Clinics* is $6.00 per issue. All prices are subject to change without notice. POSTMASTER: Send address changes to *The Psychiatric Clinics of North America,* W.B. Saunders Company, Periodicals Fulfillment, Orlando, FL 32887–4800.

Customer Service: 1-800-654-2452

The editor of this publication is Lesley Kramer Day, and the production editor is Angela Martello, W.B. Saunders Company, The Curtis Center, Independence Square West, Philadelphia, Pennsylvania 19106-3399.

Printed in the United States of America.

 0193-953X/94 $0.00 + .20

PSYCHOBIOLOGIC RESEARCH IN POST-TRAUMATIC STRESS DISORDER

Steven M. Southwick, MD, Douglas Bremner, MD, John H. Krystal, MD, and Dennis S. Charney, MD

During World War I, the term *shell shock* was used to describe symptomatic veterans who returned from war in a hyperaroused, vigilant, and agitated state. It was believed by some that brain structure was actually altered by the physical shock from exploding shells. In 1918, Meakins and Wilson,[60] in a laboratory setting, exposed shell-shocked veterans to gunfire and sulfuric flames. Compared with healthy controls, the shell-shocked veterans showed exaggerated increases in heart rate and respiratory rate. Similarly, when Fraser and Wilson[24] administered intravenous epinephrine to combat soldiers with shell shock, they also showed augmented arousal responses with marked increases in heart rate, blood pressure, and subjective anxiety.

In the 1940s, Kardiner[39] coined the term *physioneurosis* to describe the physiologic hyperarousal resulting from severe psychological trauma. For Kardiner, this was a neurosis with a profound underlying physiologic basis. Similarly, Grinker and Spiegel[27] described a "chronic stimulation of the sympathetic nervous system" that made individuals "react as if they had received an injection of adrenaline." In fact, some clinicians and researchers were so convinced that symptoms of combat neurosis were caused by altered catecholamine function that bilateral denervation of the adrenal glands was advocated as a form of treatment for highly symptomatic war veterans.[15]

After World War II, interest in the biologic basis of traumatic stress seemed to diminish. In 1980, however, when post-traumatic stress disorder (PTSD) was included in DSM-III as a formal psychiatric disorder, biologic studies began to increase in frequency. Since 1980, psychophysiologic, hormonal, neurotransmit-

From the Department of Psychiatry, Yale University School of Medicine, New Haven; and the Veterans Affairs Medical Center, West Haven, Connecticut

ter, receptor binding, electrophysiologic, and brain imaging studies have all contributed to our current understanding of the biologic underpinnings of PTSD.

In this article, we primarily focus on hormone and neurotransmitter dysregulation in PTSD. We then focus on three biologic processes that appear to be particularly relevant to PTSD. These include fear-conditioning, behavioral sensitization, and neural mechanisms involved in learning and memory. Finally, we discuss implications for therapy. Because this article is brief, we address only a portion of what is now known about the neurobiology of traumatic stress.

NEUROBIOLOGIC RESPONSE TO DANGER

When an organism is threatened, multiple neurobiologic systems become activated. It has been hypothesized that the parallel activation of various brain regions and neurotransmitter systems represents an adaptive response that is critical for survival.[12] The behavioral effects of these activated systems are complicated and incompletely understood. There is accumulating evidence, however, to suggest that a variety of neurotransmitters and hormones are important mediators in the development of anxiety and fear as well as the subsequent behavioral *fight or flight* responses that protect the organism from impending danger. More specifically, norepinephrine appears to play an important role in orienting to novel stimuli, selective attention, hypervigilance, autonomic arousal (i.e., increased blood pressure and pulse), and fear.[4] Secretion of cortisol stimulates the activation of metabolic processes necessary for sustained physical demands and tissue repair. The release of opiates tends to increase pain threshold, particularly when injury has occurred.[29, 70] The resultant diminished sensation of pain allows the organism to focus its attention on a variety of behaviors that are necessary for survival. Norepinephrine and opiates also play a critical role in the encoding of memories that may aid in recognition and response to future dangers.[58, 59]

It is important to note that other neurotransmitter systems, including the serotoninergic, dopaminergic, and benzodiazepine systems, are also critically involved in the fight-flight response.[7, 12, 82] Further, because neurotransmitter systems are closely interrelated, it is difficult, if not impossible, to determine accurately the specific behavioral effects of a single neurotransmitter system. For example, the corticotropin-releasing hormone and noradrenergic systems appear to modulate one another during acute stress. Norepinephrine turnover is increased in several forebrain areas by intracerebral ventricular infusion of corticotropin-releasing factor and stressors that activate norepinephrine (NE) neurons markedly increase corticotropin-releasing factor concentrations in the locus coeruleus. Thus, during acute stress, the hypothalamic-pituitary-adrenal (HPA) and NE systems may participate in a mutually reinforcing feedback loop.[5, 54, 91]

Although the acute neurobiologic response to trauma generally serves a protective role, it appears that chronic responses, for some individuals, may become maladaptive. For example, it has been suggested that PTSD-related symptoms, such as chronic hyperarousal, recurrent intrusive memories, impulsivity, and numbing, develop in response to trauma-induced dysregulation of multiple neurobiologic systems.[12, 82] Dysregulated neurotransmitter systems may even help to explain the high rates of substance abuse among individuals with PTSD.

NOREPINEPHRINE

Noradrenergic brain systems appear to play a role in vigilance, selective attention, and orienting behaviors.[4] Further, they are important mediators of

cardiovascular responses to life-threatening situations. Stressful or fearful stimuli of many types produce marked increases in central and peripheral NE. Selective regional increases in NE turnover and release have been observed in the locus coeruleus, limbic regions (hypothalamic, hippocampus, and amygdala), and the cerebral cortex.[32, 87, 88] The locus coeruleus is particularly relevant to catecholamine systems because it contains the majority of the brain's nonadrenergic cell bodies. An example of stress-induced noradrenergic activation comes from a study in freely moving cats, in which confrontation with threatening stimuli, such as a dog or an aggressive cat, causes a twofold to threefold increase in locus coeruleus firing, whereas confrontation with a nonthreatening novel stimulus, such as a mouse, causes no specific increase in activation.[48]

Although it is normal for NE to increase under conditions of acute stress, there is emerging evidence demonstrating that certain types of stress, especially uncontrollable stress, can cause chronic maladaptive alterations in catecholaminergic systems. For example, a series of preclinical investigations have shown that uncontrollable stress can cause a chronic increased responsivity of locus coeruleus neurons to excitatory stimulation.[77, 78] The increased responsivity has been associated with alpha$_2$-adrenergic receptor subsensitivity as well as decreased postsynaptic beta-adrenergic receptor number.[90, 99]

Clinical investigators also have noted an association between noradrenergic activity, sympathetic nervous system dysregulation, and symptoms of severe stress. Over the past 15 years, heightened sympathetic nervous system arousal has been repeatedly documented in combat veterans suffering from PTSD. Exaggerated increases in heart rate during exposure to visual and auditory combat-related stimuli have been reported in combat veterans compared with normal controls, combat veterans without PTSD, and combat veterans with anxiety disorders other than PTSD. Further, hyperreactive responses appear relatively specific to combat-related stressful stimuli. Whether mean heart rate and blood pressure is higher in PTSD patients during the resting or baseline state currently is unclear as study results have been mixed and inconclusive. Taken together, the aforementioned physiologic studies suggest that some individuals are more susceptible than others to develop sympathetic nervous system dysregulation when exposed to combat and that noradrenergic reactivity in patients with PTSD may become sensitized or conditioned by specific trauma-related stimuli.[65]

More direct biochemical studies have also provided strong support for noradrenergic dysregulation in PTSD. Kosten et al[44] found higher urinary 24-hour NE excretion in combat veterans with PTSD than in veterans with major depression or schizophrenia. This finding has been replicated in one study[96] but not in another.[68] In contrast to urine studies, investigations of plasma NE have found no differences between Vietnam veterans with PTSD and healthy controls.[6, 57] Perry et al[67] reported a *down-regulation* of platelet alpha$_2$-adrenergic receptors in a group of patients with PTSD. It was thought that the 40% decrease in receptor number was most likely a response to chronic elevation of circulating catecholamines. Compared with healthy controls, Lerer et al[47] noted lower basal and lower isoproterenol-stimulated and forskolin-stimulated cyclic adenosine monophosphate transduction in combat veterans with PTSD. Finally, platelet monoamine oxidase activity was found to be lower in 23 subjects with PTSD and alcoholism when compared with 19 age-matched controls.[17]

In the first study to evaluate simultaneously psychophysiologic reactivity and peripheral catecholamines in combat veterans with PTSD, McFall et al[56] found a parallel rise in blood pressure, heart rate, subjective distress, and plasma epinephrine during and after a combat film. The parallel rise suggested that elevations of circulating catecholamines were related to hyperreactive physiologic responses. Similarly, Blanchard et al[6] found an increase in plasma NE after

exposure to traumatic reminders in Vietnam combat veterans but not in healthy controls.

Although most studies of noradrenergic function in PTSD have used peripheral measures of catecholamine metabolism, four investigations have provided preliminary evidence for central noradrenergic dysregulation. Rainey et al,[71] in an intravenous lactate study of seven Vietnam veterans with PTSD, found that six of seven had panic attacks, and all seven had flashbacks in response to lactate. It was not possible to determine whether the attacks were manifestations of PTSD, panic disorder, or both because all six of the patients who had panic attacks with intravenous lactate also met comorbid criteria for panic disorder. Although the precise mechanism of lactate is not known, central noradrenergic dysregulation has been suggested.

Dinan et al,[21] in a study of eight traumatized women compared with matched controls, found no difference in growth hormone response to desipramine. The desipramine–growth hormone challenge is generally thought to be a probe of postsynaptic alpha$_2$-adrenergic receptor function. Hansenne et al[28] reported on the growth hormone response to intravenous clonidine as an index of noradrenergic function in PTSD. In a 20-year-old car accident victim with PTSD, the growth hormone response to intravenous clonidine was blunted. After successful treatment with relaxation, guided imagery, and implosive techniques, a repeat clonidine challenge test showed a normal growth hormone response. The authors note that the initial blunted growth hormone response suggests heightened noradrenergic sensitivity with a possible down-regulation of noradrenergic receptors in symptomatic patients with PTSD. Normalization of the growth hormone response after improvement of PTSD symptoms further indicated that the noradrenergic disturbance was related to PTSD-specific symptoms.

Finally, as predicted from preclinical data, intravenous yohimbine caused an enhanced increase in behavioral, cardiovascular, and biochemical responses among 20 traumatized combat veterans with PTSD compared with healthy controls.[63] Although yohimbine affects multiple neurotransmitter systems, its primary effect is on the noradrenergic system, where it acts as an alpha$_2$-adrenergic receptor antagonist. Infusion of yohimbine causes a brief decrease in presynaptic negative feedback, with a resultant increase in the release of NE. In the PTSD group, 70% experienced a panic attack and 40% a flashback on their active yohimbine day. This finding contrasts with reports involving patients with schizophrenia, major depression, obsessive-compulsive disorder, and generalized anxiety disorder, in whom yohimbine rarely causes panic attacks.[14] The 70% panic attack rate in PTSD patients, however, closely resembles the experience in panic disorder patients,[13] leading to the possibility that PTSD and panic disorder share a common neurobiologic abnormality related to the noradrenergic system.[83] Because yohimbine-induced panic attacks were experienced by PTSD patients both with and without comorbid panic disorder, comorbid panic disorder could not solely account for the response seen among the PTSD patients. In the aggregate, the aforementioned studies point to an increased responsivity of the sympathetic nervous system in severely traumatized combat veterans with PTSD. This responsivity appears to be more easily detected when the individual is stressed or stimulated than during basal resting states.

HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

Many types of acute stress cause increases in adrenocorticotropic hormone (ACTH) and cortisol.[55] Although NE appears to prepare the organism for action,

it is generally believed that cortisol serves a metabolic preservative function. Glucocorticoids also exert negative feedback on the HPA axis that maintains hormone levels within a nontoxic range. In animals, it has been shown that excessive elevation of glucocorticoids may have neurotoxic effects on hippocampal neurons, possibly leading to chronic learning deficits.[74, 89] Possibly consistent with this finding, patients with combat-related PTSD have been found to have deficits in short-term memory compared with matched controls.[8]

Although the HPA axis becomes activated during acute stress, the typical response to chronic stress is less clear. Some investigators have reported decreased secretion of ACTH and cortisol, whereas others have found augmented secretion.[1, 30, 38] Currently it is not known under which specific conditions augmentation occurs as opposed to adaptation. There is evidence, however, to suggest that prior stress, intensity of stressor, and novelty of stressor may be important factors.[11, 16, 94] For example, in chronically stressed rats, Irwin et al[35] reported augmented cortisol responses to stressors, particularly in animals with prior histories of stress, and Mason[51] found in primates an increased glucocorticoid response to chronic stress when the intensity of the stressor was increased or when a novel acute stressor was superimposed on a chronic stressor.

In humans, two of three studies have reported diminished mean 24-hour urinary excretion of cortisol in patients with PTSD compared with normal controls and patients with other psychiatric disorders.[52, 68, 98] Alterations in lymphocyte glucocorticoid number and cortisol response to dexamethasone also have been found in patients with PTSD. Yehuda et al[95] reported a greater number of lymphocyte glucocorticoid receptors and an exaggerated cortisol response to dexamethasone in combat veterans with PTSD compared with normal controls. After ingesting 0.5 mg (half the normal dose) of dexamethasone, combat veterans with PTSD had significantly lower cortisol responses than normal controls.[97] This finding agreed with four other standard 1-mg dexamethasone studies that failed to show nonsuppression in PTSD patients who did not meet comorbid criteria for major depression.[97] In the aggregate, the aforementioned studies point to a possible increase in glucocorticoid receptor responsivity (an enhanced negative feedback) perhaps at the level of the hypothalamus or pituitary. Such heightened negative feedback might explain diminished basal cortisol excretion, enhanced suppression of cortisol by dexamethasone, and Smith et al's[79] finding of blunted ACTH response to corticotropin-releasing factor in PTSD patients with normal (not abnormally high) circulating levels of cortisol.[97] Importantly the HPA axis findings in PTSD differ markedly from those reported in patients with major depression, suggesting that the two disorders differ with regard to underlying biologic pathophysiology.

OPIATES

Similar to glucocorticoids and NE, levels of endogenous opioids increase markedly during acute uncontrollable stress. This release of opiates appears to cause a substantial degree of analgesia in both animals and humans.[2, 29, 70] A relationship between stress, opiates, and analgesia is supported by the fact that stress-induced analgesia can be blocked by the administration of an opiate antagonist, naltrexone hydrochloride.[36, 49, 70] There is also evidence to suggest that analgesia accompanies neutral stimuli that previously have been paired with aversive stimuli.[23]

Under conditions of chronic stress, the response of the endogenous opiate

system is less well understood. On the one hand, there is evidence pointing to a continued augmentation of the opiate system over time. It appears that sensitization of the opiate system can occur so diminished levels of stress continue to cause substantial analgesia.[49] Similarly, in chronically stressed Vietnam combat veterans with PTSD, Pitman et al[70] have shown that pain threshold is significantly increased after viewing combat films. When pretreated with naloxone, film-induced analgesia is no longer observed in this population. On the other hand, in patients with chronic PTSD, there is also evidence for diminished opioid activity with lower basal levels of beta-endorphins and met-enkephalins.[31,93]

It is unclear whether alterations in endogenous opioids contribute to the symptoms seen in PTSD. Certainly elevated levels of opioids during acute stress likely contribute to the observation that pain is often muted during the acute stages of an injury. In fact, some combat veterans report feeling little or no pain when wounded in battle. With regard to chronic PTSD, it has been hypothesized that dysregulation of endogenous opioids may contribute to avoidance and numbing symptoms.[12,70]

FEAR CONDITIONING

When Kardiner and Spiegel[40] first described combat-related physioneurosis, they suggested that *conditioning* played a role in the exaggerated startle response. Similarly, Dobbs and Wilson[22] noted a "remarkable similarity" between the effects of fear conditioning in animals and the responses seen in veterans with severe war neuroses. More recently, numerous other investigations[43,76] have elaborated on the role of classic conditioning or what Kolb[43] has called the *conditioned emotional response* in the development of PTSD symptoms.

If an individual experiences a life-threatening trauma, a wide variety of stimuli that were present at the time of the trauma can become conditioned to the attendant feelings of terror and extreme anxiety. As a result, previously neutral stimuli now become capable of evoking these same feelings of terror. For example, the smell of burning firewood, a neutral stimulus, can become a conditioned stimulus for an individual who has lived through a life-threatening fire. After the fire, the smell of burning wood no longer evokes feelings of comfort and peace but instead of fear and terror. Both specific and nonspecific cues (such as the location of the trauma or the time of the trauma) that are associated with the traumatic event are capable of becoming conditioned stimuli. It also appears that stimuli similar to those associated with the trauma (stimulus generalization) can at times become conditioned stimuli. Further, it is additionally possible for a conditioned stimulus to condition other neutral stimuli that are present when the conditioned stimulus evokes a state of terror or fear (higher order conditioning). The end result may be an individual who becomes fearful and anxious in response to a wide variety of stimuli.[41–43,65]

A particularly useful model for studying fear conditioning has been the fear-potentiated acoustic startle paradigm. In this paradigm, fear and conditioned fear are measured by changes in a simple brain stem and spinal cord reflex—the acoustic startle reflex. The work of Davis[19] and others has shown that the central nucleus of the amygdala plays a critical role in fear conditioning. Noradrenergic, dopaminergic, opiate, corticotropin-releasing, and NMDA (N-methyl-D-aspartate) receptor–mediated neurochemical systems all appear to be involved.[20,62]

In humans, the abnormal startle response is a diagnostic criterion within the hyperarousal symptom cluster of DSM-III-R PTSD. Butler et al,[10] in a study of combat veterans with PTSD, found acoustic startle amplitude to be elevated in

response to moderate but not low or high levels of startle stimuli. Shalev et al[75] found no evidence of exaggerated startle in Israeli combat veterans with PTSD. As noted by Morgan et al (submitted for publication), however, alterations in startle amplitude may not clearly be seen in patients with PTSD during baseline resting states but may instead become evident during states of conditional fear. Paige et al's[66] finding of an auditory-induced reduction in cortical evoked potentials may further point to chronic abnormalities in arousal among severely traumatized veterans with PTSD.

SENSITIZATION AND STRESS SENSITIVITY

Animals that have been exposed to extreme uncontrollable stress often exhibit what has been termed *behavioral sensitization*. Behavioral sensitization refers to an enhancement of response magnitude following repeated presentations of stimuli. The time interval between the initial stimulus and subsequent stimuli appears to be an important variable. If sufficient time has passed between the initial presentation and subsequent re-exposure, a single stressful stimulus can elicit behavioral sensitization.[3]

Numerous brain regions and neurochemical systems have been implicated in the development of behavioral sensitization. Most extensively studied have been catecholamine systems. When animals are exposed to repeated stressors, dopamine beta-hydroxylase activity, tyrosine hydroxylase, and synaptic levels of NE all increase.[34, 45, 61] As a result, when animals that have been repeatedly shocked are exposed to limited shock, they respond as if the shock were much greater and release an amount of NE that is appropriate for a larger shock. Thus over time, repetitive shock appears to cause a compensatory increase in NE synthesis and subsequent release. Similarly, exposure to a potent stressor, whether single or multiple, potentiates the capacity of a subsequent stressor to increase dopamine formation in the forebrain.[11, 37]

Clinically, increased arousal, hypervigilance, insomnia, poor concentration, autonomic hyperreactivity, and exaggerated startle are all seen in patients with chronic PTSD. For some patients, these symptoms do not diminish over time but instead increase in magnitude. It has been suggested that this increase in magnitude may constitute a form of behavioral sensitization. Solomon and colleagues[80, 81] in a study of Israeli combat soldiers who fought in two successive wars, found that soldiers who developed acute combat stress reactions during the first war were more likely to become symptomatic during the second war than were soldiers who did not develop symptoms during the first war or new recruits who had never been in battle. Additionally, there is evidence to suggest that combat veterans who have been traumatized in childhood are more likely to develop PTSD after combat exposure than those who previously have not been traumatized.[9]

Behavioral sensitization may also occur in response to conditioned stimuli that previously have been paired with unconditioned stressors. Thus, neutral stimuli that have been paired with unconditioned inescapable shock are capable of causing increases in brain catecholamines and behavioral responses similar to those elicited by the original shock. For example, in freely moving cats, it has been shown that both aversive stimuli and neutral stimuli are capable of increasing locus coeruleus firing.[72]

MEMORY

PTSD is in large part a disorder of memory. Intrusive recollections of trauma in the form of recurrent daytime memories, nightmares, and flashbacks are char-

acteristic of the disorder. These intrusive recollections often remain vivid for the lifetime of the individual and can be reawakened or triggered by a variety of stimuli. Most individuals suffering from PTSD find these intrusive recollections highly distressing and in some cases tormenting. As one combat veteran put it, "it's bad enough that I had to go to Vietnam, in the first place, but to live through it over and over again is just too much."

Why are the memories associated with trauma so vivid and in some cases apparently indelible? The answer is extremely complex. Psychological, social, and biologic factors are all undoubtedly involved. From a neurobiologic perspective, animal studies have shown that fear and danger mobilize multiple neurobiologic systems. Several of these systems release neuromodulators that strongly influence the process of memory encoding and consolidation. Epinephrine, NE, and opioid peptides are three such neuromodulators.[69, 86] For example, if low-dose adrenaline is administered to rats immediately after training, long-term memory or retention is enhanced.[33, 59, 86] An elegant body of preclinical work has shown that epinephrine and endogenous opioids probably influence memory consolidation through their effects on NE.[59]

Where in the brain does this process take place? Again, the question is highly complex, but it appears that much of short-term memory consolidation takes place in the hippocampus.[63] The role of the hippocampus with regard to long-term memory, however, is diminished. It appears likely that over time memories become stored in the same areas of the cortex where sensory impressions were initially registered.[85]

The amygdala has been called a crossroads in the brain where information from all five senses is brought together and "endowed with emotional meaning."[73] The amygdala has rich connections with all cortical sensory systems (e.g., sight, smell, taste), with the thalamus, and with the hypothalamus, where it is believed that emotional responses are largely generated. The amygdala appears to orchestrate and integrate the complex interactions of sensory information, emotional tone, and neuromodulation that are necessary for the consolidation of long-term memory.

Out of the constant stream of sensory stimuli that are encountered every day, only a small amount of information is attended to and remembered. The nervous system seems to remember best those events that have an emotional impact and occur when the organism is alert, aroused, and responsive to its internal and external environment. Le Doux et al[46] have postulated that emotional memories established via thalamo-amygdala pathways may be relatively indelible. Pitman[69] has postulated that traumatic events cause an overstimulation of endogenous stress-response hormones and neuromodulators and that these substances cause an overconsolidation of memory or a *superconditioning*. This overconsolidation may account for subsequent recurrent intrusive memories.

It has been suggested that overconsolidated or indelible memories may have survival value. For self-preservation, it is critically important to remember events that occur during an aroused state of alarm that signals danger. Failure to remember such situations makes one vulnerable to similar dangers in the future.[73] The intrusive nature of memories, nightmares, and flashbacks seen in PTSD may be an unfortunate side effect or consequence of a neurobiologic mechanism that essentially serves a protective role. Dangerous situations are remembered but, unfortunately, in some cases cannot be forgotten.

Although at times these traumatic memories intrude for no apparent reason, they often occur in response to particular stimuli that evoke the memory. When an experience is first encoded into memory, all sensory and emotional aspects of the experience tend to be encoded together. The recalling of one aspect of the

experience tends to evoke all aspects of the experience. Thus, for example, the smell of burning wood in a fireplace in West Haven, Connecticut, may evoke the entire memory of a village burning 20 years ago in Vietnam. Similarly, the sight of an Asian woman walking down the street may trigger a wartime traumatic memory involving a brutal death. Of course, with that memory comes the attendant emotional terror.

IMPLICATIONS FOR TREATMENT

Many types of therapy have been used to treat PTSD.[50] Although often helpful, none have been shown to be consistently effective, and no single therapy has yet emerged as the treatment of choice. This lack of consistent therapeutic efficacy most likely stems from an incomplete understanding of underlying pathophysiology. Until the pathophysiology of a disorder is thoroughly understood, it is difficult to develop specific, effective treatments for that disorder.

With regard to pharmacologic treatments, most agents have been chosen for their known effects in treating the adjunctive symptoms of PTSD, such as depression and impulsivity, rather than for their effects on core PTSD symptoms, such as hypervigilance and intrusive memories. Further, these agents have not been targeted toward specific underlying biologic abnormalities. As a result, most medications have shown only modest effects in treating PTSD.

Among the most commonly prescribed medications for PTSD are the antidepressants. Published reports have been mixed with results ranging from marked success to little or no effect.[84] In a quantitative review that pooled data from 15 published antidepressant trials in PTSD (4 case reports, 7 open trials, 4 double-blind, placebo-controlled trials), both phenelzine and imipramine were found to have little or no effect on avoidance and hyperarousal symptoms. They did, however, cause significant improvement in re-experiencing symptoms, such as nightmares and intrusive memories. Surprisingly, coexisting depressive and anxiety symptoms showed almost no improvement, although these symptoms were often incompletely assessed. With regard to serotonin reuptake inhibitors, such as fluoxetine, there is emerging evidence that these drugs may be helpful in treating both re-experiencing and avoidance symptoms.[18, 53, 64]

Other commonly prescribed medications include benzodiazepines, neuroleptics, lithium, and carbamazepine. In general, these medications have been described as useful for specific symptoms rather than for PTSD as a whole.[25, 26] For example, lithium and carbamazepine have been used to treat impulsivity. Lithium also has been suggested for mood lability. Neuroleptics have been prescribed for severe impulsivity and psychotic-like symptoms. Unfortunately, at times these "psychotic" symptoms are actually inaccurately diagnosed re-experiencing or dissociative symptoms, such as flashbacks. Finally, benzodiazepines appear to be effective for anxiety and sleep disturbances but not for symptoms that are unique to PTSD. Finally, clonidine and propranalol have been recommended primarily for symptoms of autonomic arousal and hypervigilance.

SUMMARY

PTSD can be a chronic, devastating disorder for which treatment is only partially effective. For some, this disorder progressively worsens over time and appears to affect nearly every aspect of life, including work, interpersonal relationships, physical health, and view of self. Although generally understood as a psychological disorder, PTSD also may be viewed from a biologic perspective.

There is now accumulating evidence to suggest that severe psychological trauma can cause alterations in the organism's neurobiologic response to stress even years after the original insult.

Long-standing alterations in the biologic response to stress may contribute to a number of complaints commonly expressed by patients with PTSD. For example, increased sensitivity and sensitization of the noradrenergic system may leave the individual in a hyperaroused, vigilant, sleep-deprived, and, at times, explosive state that worsens over time. Being irritable and on edge makes it difficult to interact with family members, friends, coworkers, and employers. To quiet these symptoms of hyperarousal, PTSD patients often withdraw and use substances, particularly central nervous system depressants, that suppress peripheral and central catecholamine function. Alterations in other neurobiologic systems may further contribute to multiple symptoms, such as intrusive memories, dissociation phenomena, and even numbing.

Characterization of the biologic underpinnings of PTSD relies to a large degree on available neurobiologic technology. Much of what has been discussed in this article has grown out of advances in physiologic, hormone, and receptor assay methodology. With further advances in neurobiologic technology, in areas such as brain imaging, it soon will be possible to better delineate acute and long-term stress-induced changes in central and peripheral nervous system functioning. Undoubtedly a far richer, more complex understanding of neurobiologic responses and alterations will emerge in the near future. It is believed that an improved neurobiologic understanding will facilitate the development of more specific, effective treatments for individuals who have been severely traumatized.

ACKNOWLEDGMENT

The authors wish to thank John Mason, MD, and Rachel Yehuda, MD, for their valuable assistance, and Judy Buda and Evelyn Testa for manuscript preparation.

References

1. Amasio A, Castellanos JM, Balasch J: Adaptation of anterior pituitary hormones to chronic noise stress in male cats. Behav Neural Biol 41:71–76, 1984
2. Amir S, Brown ZA, Amit Z: The role of endorphins in stress: Evidence and speculations. Neurosci Biobehav Rev 4:77–86, 1986
3. Antelman SM: Time dependent sensitization as the cornerstone for a new approach to pharmacotherapy: Drugs as foreign or stressful stimuli. Drug Dev Res 4:1–30, 1988
4. Aston-Jones G: Locus coeruleus, stress, and post traumatic stress disorder: Neurobiological and clinical parallels. *In* Murburg M (ed): Catecholamine Function in Post Traumatic Stress Disorder, Emerging Concepts. Washington, DC, American Psychiatric Press, in press
5. Avanzino GL, Ermirio R, Cogo CE, et al: Effects of corticosterone on neurones of the locus coeruleus in the cat. Neurosci Lett 80:85–88, 1987
6. Blanchard EB, Kolb LC, Prins A, et al: Changes in plasma norepinephrine to combat-related stimuli among Vietnam veterans with post traumatic stress disorder. J Nerv Ment Dis 179:371–373, 1991
7. Bremner JD, Davis M, Southwick SM, et al: Neurobiology of post traumatic stress disorder. *In* Oldman JM, Riba MG, Tasman A (eds): Review of Psychiatry. Washington, DC, American Psychiatric Press, 1993, p 183
8. Bremner JD, Scott TM, Delaney RC, et al: Deficits in short term memory in post traumatic memory. Am J Psychiatry 150:1015–1019, 1993
9. Bremner JD, Southwick SM, Johnson DR, et al: Childhood abuse in combat-related post traumatic stress disorder. Am J Psychiatry 150:235–239, 1993

10. Butler RW, Braff DC, Rausch JL, et al: Physiological evidence of exaggerated startle response in a subgroup of Vietnam veterans with combat-related PTSD. Am J Psychiatry 147:1308–1312, 1990
11. Caggiula AR, Antelman SM, Aul E, et al: Prior stress attenuates the analgesic response but sensitizes the corticosterone and cortical dopamine responses to stress 10 days later. Psychopharmacology 99:233–237, 1989
12. Charney D, Deutch A, Krystal J, et al: Psychobiologic mechanisms of posttraumatic stress disorder. Arch Gen Psychiatry 50:294–305, 1993
13. Charney DS, Woods SW, Goodman WK, et al: Neurobiological mechanisms of panic anxiety: Biochemical and behavioral correlates of yohimbine-induced panic attacks. Am J Psychiatry 144:1030–1036, 1987
14. Charney DS, Woods SW, Price LH: Noradrenergic dysregulation in panic disorder. *In* Ballenger JC (ed): Neurobiology of Panic Disorder. New York, Wiley Liss, 1990, p 91
15. Crille G: Results of 152 denervations of the adrenal glands in the treatment of neurocirculatory asthenia. Milit Surgeon 87:509–513, 1940
16. Dallman MF, Jones MT: Corticosteroid feedback control of ACTH secretions: Effect of stress-induced corticosterone secretion on subsequent stress responses in the rat. Endocrinology 92:1367–1375, 1973
17. Davidson J, Lipper S, Kilts CD, et al: Platelet MAO activity in posttraumatic stress disorder. Am J Psychiatry 142:1341–1343, 1985
18. Davidson JRT, Roth S, Newman E: Fluoxetine in post traumatic stress disorder. J Traum Stress 4:419–423, 1991
19. Davis M: Analysis of aversion memories using the fear potentiated startle paradigm. *In* Butters N, Squire LR (eds): The Neuropsychology of Memory, ed 2. New York, Guilford Press, 1992
20. Davis M: Pharmacological and anatomical analysis of fear conditioning using the fear-potentiated startle paradigm. Behav Neurosci 100:814–824, 1986
21. Dinan TG, Barry S, Yatham LN, et al: A pilot study of a neuroendocrine test battery in posttraumatic stress disorder. Biol Psychiatry 28:665–672, 1990
22. Dobbs D, Wilson WP: Observations on persistence of war neuroses. Dis Nerv Syst 21:686–691, 1960
23. Fanselow MS: Conditioned fear-induced opiate analgesia: A competing motivational state theory of stress analgesia. Ann NY Acad Sci 467:40–54, 1986
24. Fraser F, Wilson EM: The sympathetic nervous system and the "irritable heart of soldiers." BMJ 2:27–29, 1918
25. Friedman MJ: Towards rational pharmacotherapy for post traumatic stress disorder. Am J Psychiatry 145:281–285, 1988
26. Friedman MJ: Biological approaches to the diagnosis and treatment of post traumatic stress disorder. J Traum Stress 4:67–81, 1991
27. Grinker RR, Spiegel JP: Men Under Stress. Philadelphia, Blakiston, 1945
28. Hansenne M, Pitchot W, Ansseau M: The clonidine test in post traumatic stress disorder. Am J Psychiatry 148:810–811, 1991
29. Hemingway RB, Reigle TG: The involvement of endogenous opiate systems in learned helplessness and stress-induced analgesia. Psychopharmacology 93:353–357, 1987
30. Hennessy MB, Levine S: Effects of various habituation procedures on pituitary adrenal responsiveness in the mouse. Physiol Behav 18:199–202, 1977
31. Hoffman L, Watgson PD, Wilson G, et al: Low plasma beta-endorphin in post-traumatic stress disorder. Aust NZ J Psychiatry 23:269–273, 1989
32. Ida Y, Tanaka M, Tsuda AS, et al: Attenuating effect of diazepam on stress-induced increases in noradrenaline turnover in specific brain regions of rats: Antagonism by Ro15-1788. Life Sci 37:2491–2498, 1985
33. Introini-Collison IB, McCaugh JC: Epinephrine modulates long-term retention of an aversively-motivated discrimination task. Behav Neurol Biol 45:358–365, 1986
34. Irwin J, Ahluwalia P, Anismar H: Sensitization of norepinephrine activity following acute and chronic footshock. Brain Res 379:98–103, 1986
35. Irwin J, Ahluwalia P, Zacharko RM, et al: Central norepinephrine and plasma corticosterone following acute and chronic stressors: Influence of social isolation and handling. Pharmacol Biochem Behav 24:1151–1154, 1986
36. Jackson RL, Maier SF, Coon DI: Long term analgesic effects of inescapable shock and learned helplessness. Science 206:91–93, 1979

37. Kalivas PW, Duffy P: Similar effects of daily cocaine and stress on mesocorticolimbic dopamine neurotransmission in the rat. Biol Psychiatry 25:913–928, 1989
38. Kant GJ, Leu JR, Anderson SM, et al: Effects of chronic stress on plasma corticosterone, ACTH, and prolactin. Physiol Behav 40:775–779, 1987
39. Kardiner A: The traumatic neuroses of war. *In* Psychosomatic Medicine Monograph (I–II). Washington, DC, National Research Council, 1941
40. Kardiner A, Spiegel H: The Traumatic Neuroses of War. New York, Paul Hoeber, 1947
41. Keene TM, Fairbank JP, Caddell JM: A behavioral approach to assessing and treating post traumatic stress disorder in Vietnam veterans. *In* Figley CR (ed): Trauma and Its Wake, The Study and Treatment of Post-Traumatic Stress Disorder. New York, Brunner/Mazel, 1985, pp 257–294
42. Kilpatrick DG, Veronen LJ, Best CC: Factors predicting psychological distress among rape victims. *In* Figley CR (ed): Trauma and Its Wake, The Study and Treatment of Post-Traumatic Stress Disorder. New York, Brunner/Mazel, 1985, pp 113–141
43. Kolb LC: A neuropsychological hypotheses explaining post traumatic stress disorders. Am J Psychiatry 144:989–995, 1987
44. Kosten TR, Mason JW, Giller EL, et al: Sustained urinary norepinephrine and epinephrine elevation in post-traumatic stress disorder. Psychoneuroendocrinology 12:13–20, 1987
45. Kramarcy NR, Delaney RL, Dunn AL: Footshock treatment activates catecholamine synthesis in slices of mouse brain regions. Brain Res 290:311–319, 1984
46. LeDoux JE, Romanski L, Xagoraris A: Indelibility of subcortical emotional memories. J Cogn Neurosci 1:238–243, 1989
47. Lerer B, Bleich A, Kotler M: Posttraumatic stress disorder in Israeli combat veterans. Arch Gen Psychiatry 44:976–981, 1987
48. Levine ES, Litto WJ, Jacobs BL: Activity of cat locus coeruleus noradrenergic neurons during the defense reaction. Brain Res 531:189–195, 1990
49. Maier SF: Stressor controllability and stress induced analgesia. Ann NY Acad Sci 467:55–72, 1986
50. Marmar CR, Foy D, Kayan RS, et al: An integrated approach for treating post traumatic stress disorder. *In* Oldham JM, Riba MB, Tasman A (eds): Review of Psychiatry. Washington, DC, American Psychiatric Press, 1993, p 239
51. Mason JW: A review of psychoendocrine research on the sympathetic-adrenal medullary system. Psychosom Med 30:631–653, 1968
52. Mason JW, Giller EL, Kosten TR, et al: Elevation of urinary norepinephrine/cortisol ratio in post traumatic stress disorder. J Nerv Ment Dis 176:498–502, 1988
53. McDougle C, Southwick SM, Charney DS, et al: An open trial of fluoxetine in the treatment of post traumatic stress disorder. J Clin Psychopharmacol 1:325–327, 1991
54. McEwen BS: Glucocorticoid-biogenic amine interactions in relation to mood and behavior. Biochem Pharmacol 36:1755–1763, 1987
55. McEwen BS, DeKloet ER, Rostene W: Adrenal steroid receptors and actions in the nervous system. Physiol Rev 66:1121–1188, 1986
56. McFall M, Murburg M, Ko G, et al: Autonomic responses to stress in Vietnam combat veterans with post-traumatic stress disorder. Biol Psychiatry 27:1165–1175, 1990
57. McFall ME, Vaith RC, Murburg MM: Basal sympathoadrenal function in post traumatic stress disorder. Biol Psychiatry 31:1050–1056, 1992
58. McGaugh JL: Involvement of hormonal and neuromodulatory systems in the regulation of memory storage. Ann Rev Neurosci 2:255–287, 1989
59. McGaugh JL: Significance and remembrance: The role of neuromodulatory systems. Psychol Sci 1:15–25, 1990
60. Meakins JC, Wilson RM: The effect of certain sensory stimulation on the respiratory rate in cases of so-called "irritable heart." Heart 7:17–22, 1918
61. Melia KR, Nestler EJ, Haycock J, et al: Regulation of tyrosine hydroxylase (TH) in the locus coeruleus (LC) by corticotropin-releasing factor (CRF): Relation to stress and depression. Neurosci Abstr 16:444, 1991
62. Miserendino MJD, Sananes CB, Melia KR, et al: Blocking of aquisition but not expression of fear potentiates startle by NMDA antagonists in the amygdala. Nature 345:716–718, 1990
63. Mishkin M, Appenzeller T: The anatomy of memory. Sci Am 256:80–89, 1987

64. Nagy LM, Morgan CA, Southwick SM, et al: Open prospective trial of fluoxetine for post traumatic stress disorder. J Clin Psychopharmacol 13:107–113, 1993
65. Orr SP: Psychophysiologic studies of post traumatic stress disorder. *In* Giller EL (ed): Biological Assessment and Treatment of Post Traumatic Stress Disorder. Washington, DC, American Psychiatric Press, 1990, p 135
66. Paige S, Reid G, Allen M: Psychophysiological correlates of post traumatic stress disorder. Biol Psychiatry 27:419–430, 1990
67. Perry BD, Southwick SM, Yehuda R: Adrenergic dysregulation in PTSD. *In* Giller EL (ed): Biological Assessment and Treatment of Post Traumatic Stress Disorder. Washington, DC, American Psychiatric Press, 1990, p 87
68. Pitman R, Orr S: Twenty-four hour urinary cortisol and catecholamine excretion in combat-related posttraumatic stress disorder. Biol Psychiatry 27:245–247, 1990
69. Pitman RK: Posttraumatic stress disorder hormones, and memory [edit]. Biol Psychiatry 26:221–223, 1989
70. Pitman RK, van der kolk BA, Orr SP, et al: Naloxone-reversible analgesic response to combat-related stimuli in post traumatic stress disorder. Arch Gen Psychiatry 47:541–544, 1990
71. Rainey JM, Aleem A, Ortiz A, et al: A laboratory procedure for the induction of flashbacks. Am J Psychiatry 144:1317–1319, 1987
72. Rasmussen K, Marilak DA, Jacobs BL: Single unit activity of the locus coeruleus in the freely moving cat, I. During naturalistic behaviors and in response to simple and complex stimuli. Brain Res 371:476–488, 1987
73. Reiser M: Memories in Mind and Brain: What Dream Imaging Reveals. New York, Basic Books, 1991
74. Sapolsky RM, Uno H, Rebert CS, et al: Hippocampal damage associated with prolonged glucocorticoid exposure in primates. J Neurosci 10:2897–2902, 1990
75. Shalev AY, Orr SP, Peri T, et al: Physiologic responses to loud tones in Israeli patients with post traumatic stress disorder. Arch Gen Psychiatry 49:870–875, 1992
76. Shalev AY, Rogel-Fuchs Y, Pitman R: Conditioned fear and psychological trauma. Biol Psychiatry 31:863–865, 1991
77. Simson PE, Weiss JM: Altered activity of the locus coeruleus in an animal model of depression. Neuropsychopharmacology 1:287–295, 1988
78. Simson PE, Weiss JM: Responsiveness of locus coeruleus neurons to excitatory stimulation is uniquely regulated by alpha-2 receptors. Psychopharmacol Bull 24:349–354, 1988
79. Smith MA, Davidson J, Ritchie JC, et al: The corticotropin releasing hormone test in patients with post traumatic stress disorder. Biol Psychiatry 26:349–355, 1989
80. Solomon Z: Characteristic psychiatric symptomatology of post traumatic stress disorder in Veterans: A three-year follow-up. Psychol Med 19:927–936, 1989
81. Solomon Z, Mikulincer M, Jakob BR: Exposure to recurrent combat stress: Combat stress reactions among Israeli soldiers in the Lebanon War. Psychol Med 17:433–440, 1987
82. Southwick SM, Krystal JH, Johnson DR, et al: Neurobiology of post traumatic stress disorder. *In* Tasman A, Riba MG (eds): Review of Psychiatry. Washington, DC, American Psychiatric Press, 1992, p 347
83. Southwick SM, Krystal JH, Morgan AC, et al: Abnormal noradrenergic function in post traumatic stress disorder. Arch Gen Psychiatry 50:266–274, 1993
84. Southwick SM, Yehuda R, Giller E, et al: The effects of antidepressants in the treatment of post traumatic stress disorder: A quantitative review. *In* Murburgh M (ed): Catecholamines in Post-Traumatic Stress Disorder. Washington, DC, American Psychiatric Press, in press
85. Squire L: Memory and the hippocampus: A synopsis from findings with rats, monkeys and humans. Psychol Rev 99:195–231, 1992
86. Squire LR: Mechanisms of memory. Science 232:1612–1619, 1986
87. Tanaka M, Ida Y, Tsuda A, et al: Involvement of brain noradrenaline and opioid peptides in emotional changes induced by stress in rats. *In* Oomura Y (ed): Emotions: Neural and Chemical Control. Tokyo, Scientific Societies Press, 1986, p 417
88. Tsuda A, Tanaka M: Differential changes in noradrenaline turnover in specific regions of rat brain produced by controllable and uncontrollable shocks. Behav Neurosci 99:802–817, 1985

89. Uno H, Tarara R, Else J, et al: Hippocampal damage associated with prolonged and fatal stress in primates. J Neurosci 9:1705–1711, 1989
90. U'Prichard DC, Kvetnansky R: Central and peripheral adrenergic receptors in acute and repeated immobilization stress. *In* Usdin E, Kvetnansky R, Kopin IJ (eds): Catecholamines and Stress: Recent Advances. Amsterdam, Elsevier Science Publishers, 1980, p 299
91. Valentino RJ, Foote SL, Aston-Jones G: Corticotropin-releasing factor activates noradrenergic neurons of the locus-coeruleus. Brain Res 270:363–367, 1983
92. van der Kolk R, Greenberg M, Boyd H, et al: Inescapable shock, neurotransmitters, and addiction to trauma toward a psychobiology of post traumatic stress. Biol Psychiatry 20:314–325, 1985
93. Wolf ME, Mosnalm AD, Puente J, et al: Methionine-enkephalin in post-traumatic stress disorder: Plasma levels and degradation. Res Commun Psychol Psychiatry Behav 15(1–2:73–78, 1990
94. Yehuda R, Giller EL, Southwick SM, et al: Hypothalamic-pituitary-adrenal dysfunction in post traumatic stress disorder. Biol Psychiatry 30:1031–1048, 1991
95. Yehuda R, Lowy MT, Southwick SM, et al: Increased number of glucocorticoid receptors in post traumatic stress disorder. Am J Psychiatry 144:499–504, 1991
96. Yehuda R, Southwick S, Giller EL, et al: Urinary catecholamine excretion and severity of PTSD symptoms in Vietnam combat veterans. J Nerv Ment Dis 180:321–325, 1992
97. Yehuda R, Southwick SM, Krystal JH: Enhanced suppression of cortisol following dexamethasone administration in post traumatic stress disorder. Am J Psychiatry 150:83–86, 1993
98. Yehuda R, Southwick S, Nussbaum G, et al: Low urinary cortisol excretion in patients with post-traumatic stress disorder. J Nerv Ment Dis 178:366–369, 1990
99. Yocca FD, Friedman E: Effect of immobilization stress on rat pinea abeta-adrenergic receptor-mediated function. J Neurochem 42:1427–1432, 1984

Address reprint requests to

Steven M. Southwick, MD
Department of Psychiatry 116/A
VA Medical Center
950 Campbell Avenue
West Haven, CT 06516